Decoding Minimal Residual Disease In Peritoneal Carcinomatosis From Colorectal Cancer: A Multi-Omic Approach

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Abstract

Background: Peritoneal carcinomatosis from colorectal cancer (PC-CRC) is a challenging disease due to its aggressive nature, complex treatment, and lack of prognostic and predictive biomarkers. Liquid biopsy is a minimally-invasive approach to explore real-time genomic landscape and investigate tumor-derived factors in blood.

Objective: To identify a multi-omic signature for minimal residual disease (MRD) detection in PC-CRC patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS + HIPEC), by integrating the analysis of circulating tumor DNA (ctDNA) in peripheral blood and peritoneal tumor DNA (ptDNA) in peritoneal fluid together with stroma-derived biomarkers from cancer-associated fibroblasts (CAFs).

Methods: PC-CRC patients treated with CRS + HIPEC at Hospital del Mar (Barcelona, Spain) were included. Serial peripheral blood samples (before and day 30 after surgery), serial peritoneal fluid samples (before and 3 days after surgery), archival and fresh tissue from paired primary tumor and peritoneal metastases were collected. ctDNA, ptDNA and tissue DNA were analyzed by a next-generation sequencing (NGS)-based approach (Oncomine, ThermoFisher). CAFs and patient-derived organoids (PDOs) were derived and characterized from fresh tissue samples.

Results: Overall, 43 microsatellites stable PC-CRC patients have been included. Left colon and rectum were the most frequent primary tumor locations (N = 17; 40%), and adenocarcinoma NOS the predominant histological type (N = 26; 60%). Median peritoneal cancer index (PCI) was 12 and the most adopted regimen for HIPEC was Cisplatin + Mitomycin-C (N = 28; 65%). NGS in tissue samples detected RAS (N = 24; 55%), TP53 (N = 7; 16%), and PIK3CA (N = 6; 14%) as the most frequent mutated genes. Concurrent mutations were observed in 13 cases. Preliminary analysis of peritoneal fluid demonstrated ptDNA detectability in 3 out of 4 cases. To date, 23 CAFs and 3 PDOs have been derived from patients included in this study.

Conclusions: Our translational research addresses the need for biomarkers in PC-CRC. We have been able to establish the workflow and the new and necessary methodology, and we anticipate enrolling up to 60 patients in the final analysis to better understand MRD after radical treatments and ultimately improve clinical outcomes in this challenging population

Do you have any conflicts of interest?

No, I do not have a conflict of interest.